

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year)

27 April 2000 (27.04.00)

International application No.

PCT/EP99/06844

Applicant's or agent's file reference

WO/381

International filing date (day/month/year)

16 September 1999 (16.09.99)

Priority date (day/month/year)

18 September 1998 (18.09.98)

Applicant

GRONE, Hermann-Joseph et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

27 March 2000 (27.03.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

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Authorized officer

Nestor Santesso

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference WO/381	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP99/06844	International filing date (day/month/year) 16/09/1999	Priority date (day/month/year) 18/09/1998	
International Patent Classification (IPC) or national classification and IPC A61K38/19			
Applicant APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 27/03/2000	Date of completion of this report 14.06.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fayos, C Telephone No. +49 89 2399 2180



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/06844

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-24 as originally filed

Claims, No.:

1-16 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 1-8 (Industrial Applicability).

because:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/06844

- ☒ the said international application, or the said claims Nos. 1-8 (Industrial Applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-8
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-8 (see separate sheet)
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

- 1- Claims 1-8, relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 2- Reference is made to the following documents:

D1: WO 97 05896 A (SCHERING CORP) 20 February 1997 (1997-02-20)

NOVELTY - Art. 33 (1) and (2) PCT

- 3- Claims 1-16 appear to be new in the light of the prior art cited in the search report and provided the restriction mentioned in item III 1- above.

3.1- None of the prior art documents cited in the search report discloses:

- the use of a chemokine receptor antagonist in combination with cyclosporin to produce a pharmaceutical composition for treating or preventing the rejection of transplanted organs, tissues or cells (claims 1-7)

and

- a pharmaceutical composition containing a chemokine receptor antagonist and a cyclosporin, in the presence of one or more pharmaceutically acceptable excipients, for treating or preventing the rejection of transplanted organs, tissues or cells (claims 9-16).

Therefore, claims 1-16 can be considered as being new in the light of the prior art cited in the search report and provided the restriction mentioned in item III 1- above.

INVENTIVE STEP - Art. 33 (1) and (3) PCT

- 4- The problem posed in the present application is to provide means for treating or preventing rejection of transplanted organs, tissues or cells.
- 4.1- The solution proposed in the present application is the use of a chemokine receptor antagonist, together with a cyclosporin, and the experimental data of the description show that the combination of a chemokine receptor antagonist (Met-RANTES), together with a cyclosporin (cyclosporin A) has a synergetic effect.
- 4.2- D1 discloses a method of suppressing (among others) graft/tissue rejection by means of the combined use of IL-10 and cyclosporine (p 1 §1).
D1 is therefore the closest prior art.
- 4.3- D1 states (p 6 § 1-2) that the combined/concurrent administration of IL-10 and cyclosporin A (or cyclosporin A analogue) causes a **synergistic** suppression of T cell proliferation and therefore can be used in the suppression of pathology associated with T cell responses, in particular tissue graft rejection. As mentioned in D1, **interleukin 10 (IL-10)**, a cytokine produced by T lymphocytes, was first identified by its ability to **inhibit interferon gamma (IFN- γ) and IL-2 synthesis** by mouse and human **T lymphocytes**. IL-10 exerts a wide range of effects on a variety of cell types. IL-10 inhibits the synthesis of a wide spectrum of cytokines produced by T cells and monocytes. In addition to **inhibiting the synthesis of IFN- γ and IL-2**, **IL-10** has also been shown to **inhibit production of the monokines IL-1 α , IL-1 β ,**

IL-6 and TNFa.

5- Claims 1-16 appear to be inventive in the light of the prior art cited in the search report

- 5.1- Nothing in D1 alone, or in combination with the other prior art documents cited in the search report, appears to suggest that the synergetic effect achieved by the combination of IL-10 and cyclosporine A could be due to the ability of IL-10 to indirectly inhibit RANTES or other related chemokines (see 4.3- above).

[IL-10 exerts a wide range of effects on a variety of cell types and inhibits the synthesis of a wide spectrum of cytokines produced by T cells and monocytes. In addition to inhibiting the synthesis of IFN- γ and IL-2, IL-10 has also been shown to inhibit production of the monokines IL-1a, IL-1P, IL-6 and TNFa. It is also known (p 15 lines 22-25) that some of the cytokines involved in renal transplant rejection are responsible for RANTES stimulation (TNF-a, IL-1b, TNF-b, IFN- γ), and thus the inhibition of their synthesis by IL-10 inhibits the stimulation of RANTES (through the inhibition of IFN- γ and IL-2 synthesis, and consequently the inhibition of TNF-a, IL-1 b, TNF-b and IFN- γ).]

Hence, claims 1-16 appear to involve an inventive step in the light of the prior art cited in the search report.

INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT

- 6- For the assessment of the present claims 1-8 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

- 7- Claim 10 comprises all the features of claim 9 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).
- 8- There appears to be an inconsistency in the disclosure of claims 8 and 16: "treating or preventing renal allograft transplantation". It is believed (and supported by the description on e. g. p 6 lines 1-3) that the applicant meant: "treating or preventing rejection of renal allograft transplantation".

Hence, claims 8 and 16 have been read as if they were directed to the treatment and prevention of rejection of renal allograft transplantation.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference W0/381	FOR FURTHER ACTION		see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.
International application No. PCT/EP 99/ 06844	International filing date (day/month/year) 16/09/1999	(Earliest) Priority Date (day/month/year) 18/09/1998	
Applicant APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. et al.			

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ **None of the figures.**

INTERNATIONAL SEARCH REPORT

International Application No.

T/EP 99/06844

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K38/19 A61K38/13 //(A61K38/19, 38:13)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 97 05896 A (SCHERING CORP) 20 February 1997 (1997-02-20) the whole document	1, 2, 9, 10 6-8, 14-16
A	WO 98 06751 A (RES CORP TECHNOLOGIES INC) 19 February 1998 (1998-02-19) cited in the application abstract page 4, line 5 -page 5, line 27; claims 14-22 -/-	1-3, 8-11, 16



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

29 November 1999

Date of mailing of the international search report

15/12/1999

Name and mailing address of the ISA

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Stein, A

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 99/06844

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 17935 A (GLAXO GROUP LTD ;WELLS TIMOTHY NIGEL CARL (CH); PROUDFOOT AMANDA E) 13 June 1996 (1996-06-13) cited in the application abstract page 1, line 27 -page 3, line 4 page 4, line 26 - line 30 page 6, line 27 -page 7, line 3 page 14, line 1 -page 16, line 11	1,2,4,5, 8-10,12, 13,16
A	WO 98 06703 A (CONNOR DAVID THOMAS ;WARNER LAMBERT CO (US); GLASE SHELLY ANN (US)) 19 February 1998 (1998-02-19) page 1, line 1 -page 6, line 4 page 17, line 1 - line 12; claims 4,12-17	1,2, 8-10,16
A	PATTISON J M ET AL: "RANTES chemokine expression in transplant-associated accelerated atherosclerosis." JOURNAL OF HEART AND LUNG TRANSPLANTATION, (1996 DEC) 15 (12) 1194-9, XP002094329 the whole document	1-5, 8-13,16
P,X	GRONE H J ET AL: "Met- RANTES reduces vascular and tubular damage during acute renal transplant rejection: blocking monocyte arrest and recruitment." FASEB JOURNAL, (1999 AUG) 13 (11) 1371-83. , XP002124184 the whole document	1-16
P,X	NELSON P.J.: "Chemokines and chemokine receptors in renal transplant rejection." EUROPEAN CYTOKINE NETWORK, (1999) 10/2 (305-306). , XP000857302 the whole document	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/06844

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9705896	A	20-02-1997	AU 6842296 A CA 2228379 A EP 0845994 A JP 11510806 T	05-03-1997 20-02-1997 10-06-1998 21-09-1999
WO 9806751	A	19-02-1998	NONE	
WO 9617935	A	13-06-1996	AU 688641 B AU 4120896 A BR 9509890 A CA 2207036 A CN 1168697 A CZ 9701719 A EP 0796330 A FI 972433 A HU 77075 A JP 10510151 T NO 972620 A NZ 296570 A PL 320565 A	12-03-1998 26-06-1996 30-12-1997 13-06-1996 24-12-1997 12-11-1997 24-09-1997 06-06-1997 02-03-1998 06-10-1998 06-08-1997 25-11-1998 13-10-1997
WO 9806703	A	19-02-1998	AU 4054197 A EP 0927167 A	06-03-1998 07-07-1999